Heliyon 10 (2024) e32198

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Hsa-miR-342-3p and hsa-miR-360 may be the key molecules that promote periodontitis in type 2 diabetes mellitus

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ARTICLE INFO

Keywords:
Periodontitis
Type 2 diabetes mellitus
miRNA
Immune infiltration
Ras signaling pathway

ABSTRACT

Background: Periodontitis (PD) has been acknowledged as a complication associated with type 2 diabetes mellitus (T2DM). However, the precise mechanism through which T2DM fosters the development of PD remains elusive. Our objective is to elucidate the connection between these two conditions by conducting bioinformatics analysis.

Methods: In this study, we analyzed miRNA datasets pertaining to T2DM and PD sourced from GEO. Through differential expression analysis, we identified common differentially expressed miRNAs (DE-miRNAs) and subsequently analyzed the functional enrichment of these common DE-miRNAs. We further leveraged the PD transcriptome database to select DE-miRNA-targeted mRNAs and examined their association with immune infiltration. Finally, machine learning was used to further screen hub DE-miRNA-targeted mRNAs and validate our data in external datasets.

Results: Two common DE-miRNAs, namely hsa-miR-342-3p and hsa-miR-360, were identified from the miRNA datasets of PD and T2DM. Functional enrichment analysis indicated that these two common DE-miRNAs predominantly participate in Ras, PI3K-Akt, p53, and MAPK signaling pathways. Integration of the PD transcriptome dataset revealed a total of 21 DE-miRNA-targeted mRNAs in PD, with strong correlations observed with plasma cells and dendritic cells. Finally, three hub DE-miRNA-targeted mRNAs (hsa-miR-342-3p-/hsa-miR-360-RASAL2, hsa-miR-360-ENTPD1/PLXDC2) were identified. ENTPD1 exhibited a robust positive correlation with plasma cells and a negative correlation with resting dendritic cells.

Conclusions: Therefore, hsa-miR-342-3p-/hsa-miR-360-RASAL2, as well as hsa-miR-360-ENTPD1/PLXDC2, may serve as diagnostic and therapeutic targets for T2DM-associated PD.

1. Introduction

Diabetes mellitus (DM) comprises both type 1 and type 2 diabetes mellitus (T2DM), constituting a group of metabolic diseases primarily resulting from an absolute or relative deficiency of insulin [1]. In 2017, an estimated 45.118 billion individuals worldwide were living with diabetes, a number anticipated to rise to 4.97 billion by 2045 [2]. T2DM represents 90 % of global DM cases [3]. Periodontitis (PD), characterized as a chronic, low-grade, multifactorial, inflammatory disease, is primarily caused by plaque

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https://doi.org/10.1016/j.heliyon.2024.e32198
Received 19 May 2023; Received in revised form 24 May 2024; Accepted 29 May 2024
Available online 31 May 2024

accumulation that irritates the biofilm, leading to irreversible damage to the supporting tissues around the teeth and eventual tooth loss [4,5]. As a prevalent oral noninfectious ailment, PD currently affects over half of the global population, diminishing people's quality of life and escalating the burden on national healthcare [6]. Epidemiological evidence indicates an association between PD and various diseases, including DM, cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and chronic kidney disease (CKD) [7–10].

Research demonstrates a bidirectional relationship between DM and PD [11–13]. In 2008, the American Diabetes Association categorized periodontitis as a complication of diabetes [14]. Diabetes, particularly with inadequate blood sugar control, is more likely to be associated with PD [14]. PD is also recognized as a risk factor for DM, and its control can effectively ameliorate high blood sugar levels and insulin resistance in diabetic patients [15]. Mechanistically, the heightened expression of inflammatory factors and increased glycation end products in DM can result in vascular permeability, recruitment of inflammatory cells, decreased osteoprotegerin expression, activation of matrix metalloproteinases, connective tissue destruction, increased apoptosis of stromal cells, and limited periodontal tissue repair [16]. Furthermore, the rise in reactive oxygen species (ROS) and lipid peroxides due to mitochondrial dysfunction induced by T2DM induces apoptosis and damages matrix structural components [16]. Conversely, local inflammation in PD heightens the expression of TNF-α and interleukin 14 in the circulatory system, fostering a systemic inflammatory response and subsequently leading to insulin resistance [17]. However, the precise mechanism underlying the interplay between PD and DM remains incompletely understood.

microRNA (miRNA) constitutes a class of small non-coding RNA molecules linked to various physiological and pathological changes. In recent years, several miRNAs, such as miR-205, miR-335, miR-100, and miR-125a, have been associated with PD [18]. Simultaneously, plasma miRNA is easily detectable, facilitating clinical application. Therefore, we aim to employ bioinformatics, coupled with T2DM miRNA data, PD miRNA data, and PD mRNA data, to elucidate the associated mechanism of T2DM promoting periodontitis and identify miRNAs for early diagnosis. This endeavor seeks to provide evidence for the early diagnosis and treatment of periodontitis in clinical T2DM patients.

2. Methods

2.1. Data source and acquisition

Datasets pertaining to PD and T2DM were sourced from the Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo/). The miRNA microarray dataset (GSE54710) focusing on PD included 158 samples of gingival papillae from diseased areas of PD and 40 samples from healthy areas. The miRNA microarray dataset (GSE185845) associated with T2DM comprised 20 serum-circulating miRNA samples from individuals with T2DM and 16 samples from those without T2DM. The mRNA microarray dataset (GSE16134) related to PD consisted of 241 gingival papillae samples from diseased areas and 69 samples from healthy areas. Additionally, two validation datasets for mRNA microarrays were used: the GSE10334 dataset with 183 gingival papillae samples from

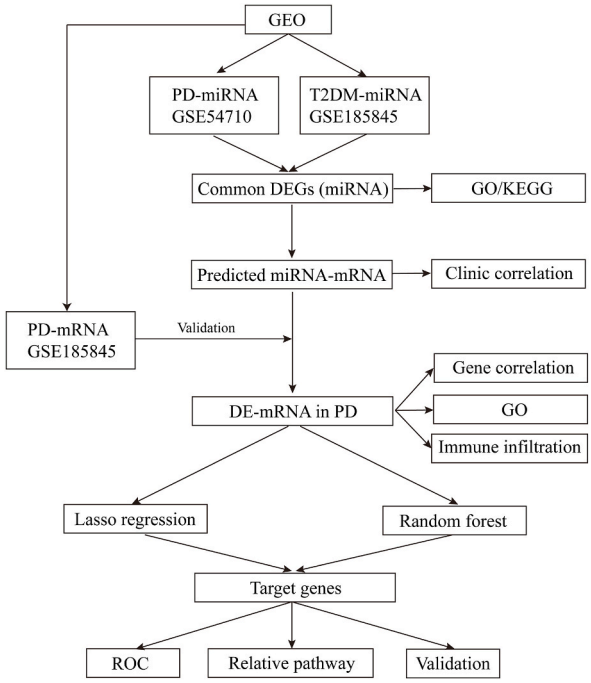

Fig. 1. Flow-chart in the study.

diseased areas of PD and 64 samples from healthy areas, and the GSE173078 dataset with 12 samples from diseased areas of PD and 12 samples from healthy areas. The study's flowchart is illustrated in Fig. 1.

2.2. miRNA-mRNA prediction

In order to understand the function of miRNAs, the downstream mRNA of the selected DE-miRNAs was predicted. Three miRNA-mRNA online databases, miRWalk (http://mirwalk.umm.uni-heidelberg.de/), TargetScanHuman 8.0 (https://www.targetscan.org/vert_80/) and miRDB (https://mirdb.org/) were employed to performed the prediction of downstream mRNA. The common predicted downstream mRNAs in three online databases were considered as the miRNA-targeted mRNA.

2.3. Differentially expressed analysis

We utilized the "limma" R package to conduct the differential expression analysis, aiming to identify differentially expressed genes (DEGs). The screening criteria were set at a P-value <0.05 and $|\log_2(FC)| > \log_2(1.2 \text{ or } 1.5)$. The outcomes of the differential expression analysis were visually represented using a volcano plot. Additionally, Venn diagrams were employed to pinpoint the common DEGs across datasets.

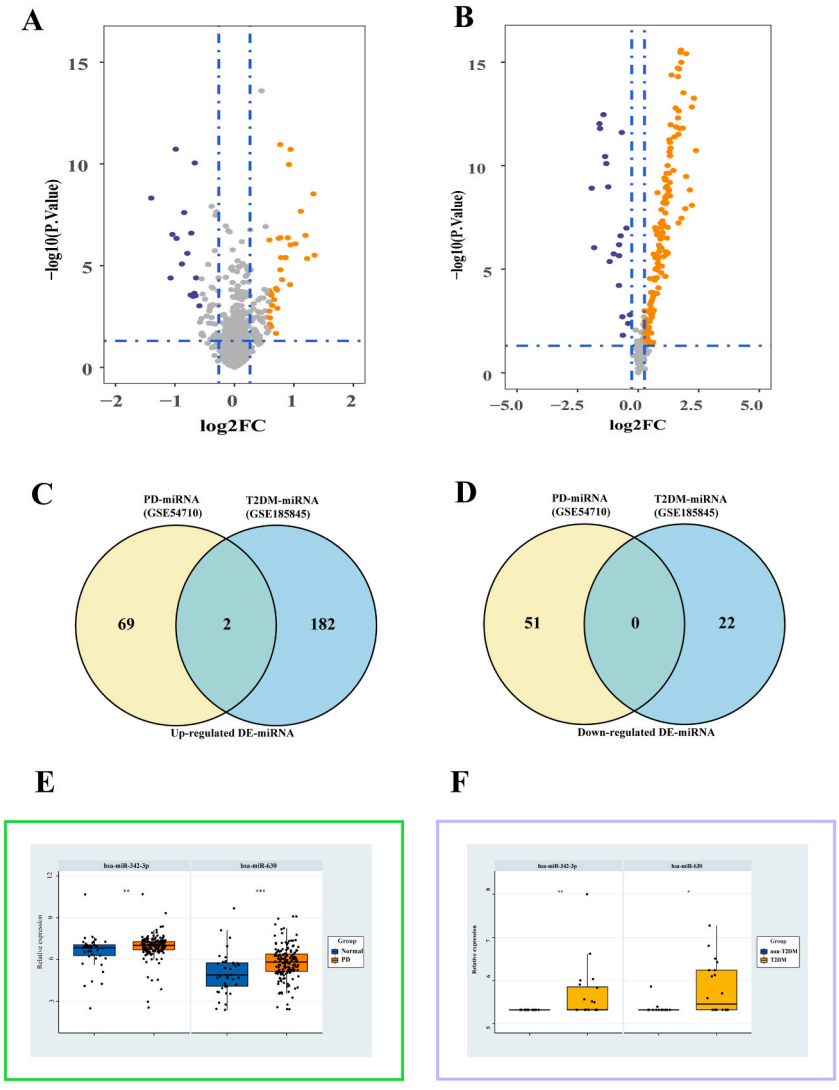

Fig. 2. Identification of common DE-miRNAs. **(A)** The volcano plot of PD DE-miRNAs; **(B)** The volcano plot of T2DM DE-mRNAs; **(C)** Venn diagram of up-regulated DE-miRNAs; **(D)** Venn diagram of down-regulated DE-miRNAs; **(E)** The relative expression of common DE-miRNAs in PD. **(F)** The relative expression of common DE-miRNAs in T2DM. *p < 0.05; **p < 0.01; ***p < 0.001.

2.4. Functional enrichment analysis

The Database for Annotation, Visualization and Integrated Discovery (DAVID, https://david.ncifcrf.gov/) and Metascape (https://metascape.org/gp/index.html#/main/step1) are online functional annotation tools to identify the functional enrichment of DEGs [19]. The functional enrichment analysis encompasses gene ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG). GO analysis categorizes functions into biological process (BP), molecular function (MF), and cellular component (CC). The outcomes of GO enrichment analysis and KEGG pathway analysis were visualized using R software, with statistical significance set at a p-value <0.05.

2.5. Machine learning

The least absolute shrinkage and selection operator (Lasso) regression [20] and random forest (RF) [21] were employed to performed the screening of hub genes from predicted mRNA which was verified by PD mRNA dataset. Lasso regression was conducted by "glmnet" R package and lambda.min was chosen as the optimal lambda. RF was performed by "randomForest" R package. The intersection genes of Lasso and RF was considered as hub genes.

2.6. Immune infiltration analysis and ROC curve

CIBERSORT was an algorithm used to identify the proportion of different immune cells between two group [22]. We employed the "Cibersort" R package to analyze immune cell infiltration in PD and elucidate the connection between hub genes and immune cells. To assess the diagnostic effectiveness of various target genes, we conducted Receiver Operating Characteristic (ROC) curve analysis using the online tool "Hiplot," with the Area Under the Curve (AUC) serving as a comparative metric.

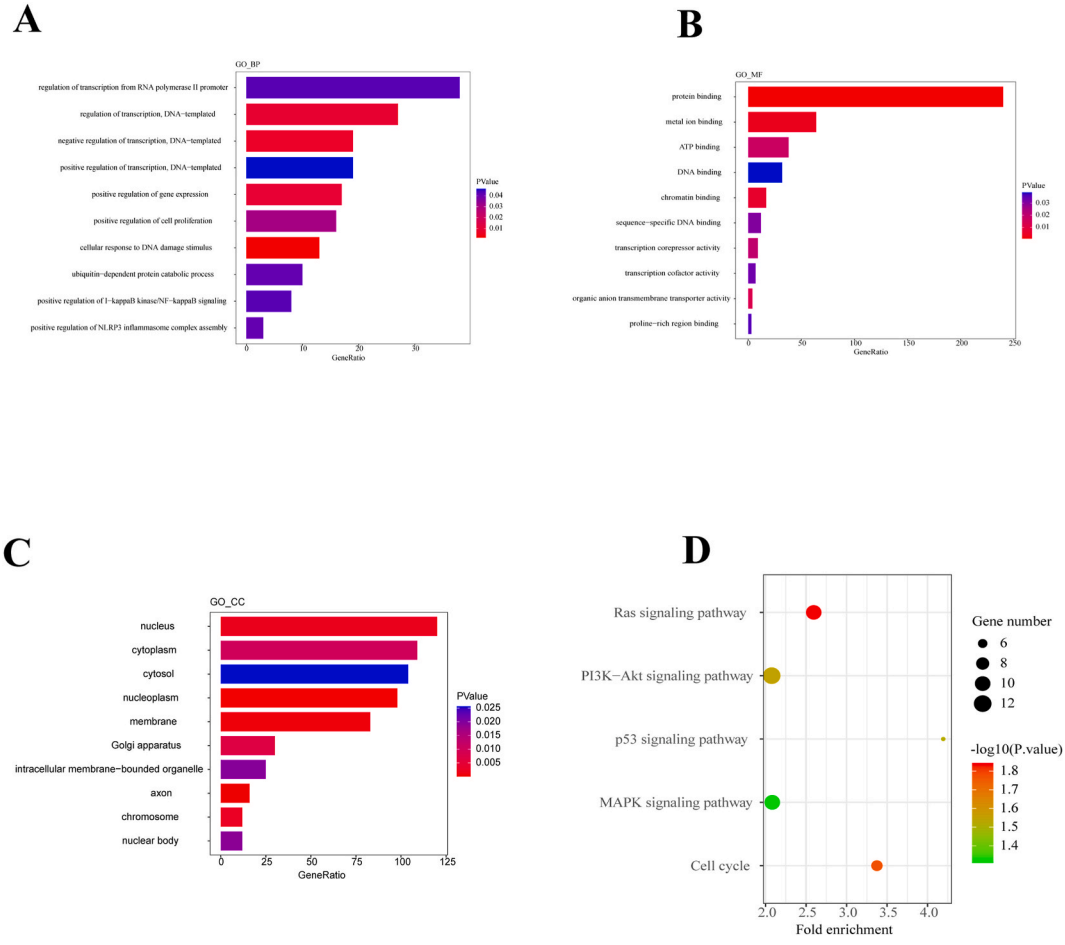

Fig. 3. The functional enrichment analysis of common DE-miRNAs. **(A)** Top 10 GO BP terms of common DE-miRNAs. **(B)** Top 10 GO MF terms of common DE-miRNAs. **(C)** Top 10 GO CC terms of common DE-miRNAs. **(D)** KEGG pathways of common DE-miRNAs.

2.7. Statistical analysis

Statistical analyses were conducted using R software. The comparison between two samples was executed using a two-sample *t*-test, while correlations were assessed using Spearman's correlation. A P-value <0.05 was deemed statistically significant.

3. Results

3.1. Identification of DE-miRNAs between PD and T2DM

We identified 71 up-regulated and 51 down-regulated DE-miRNAs in gingival papillae samples from PD, along with 184 up-regulated and 22 down-regulated DE-miRNAs in serum-circulation samples from T2DM (Fig. 2A and B). Intersection analysis of up-regulated and down-regulated DE-miRNAs yielded 2 common DE-miRNAs, namely hsa-miR-342-3p and hsa-miR-630 (Fig. 2C and D). The relative expression of these two DE-miRNAs in PD and T2DM datasets is illustrated in Fig. 2E and F, respectively.

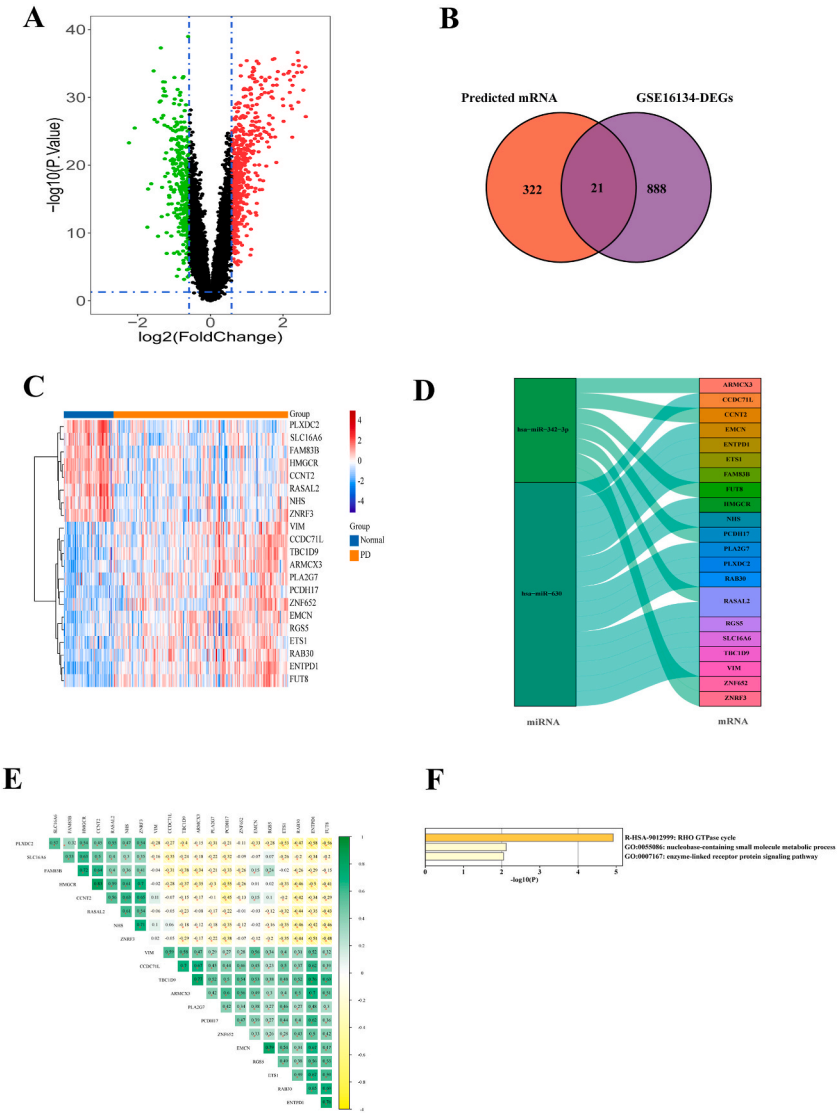

Fig. 4. Identification of DE-miRNA-targeted mRNAs. **(A)** The volcano plot of PD DEGs. **(B)** Venn diagram of predicted miRNA-targeted mRNAs and PD DEGs. **(C)** The heatmap of 21 DE-miRNA-targeted mRNAs. **(D)** Sankey map of DE-miRNAs and 21 DE-miRNA-targeted mRNAs. **(E)** Correlation diagram of 21 DE-miRNA-targeted mRNAs. **(F)** GO terms of 21 DE-miRNA-targeted mRNAs.

3.2. Functional enrichment of DE-miRNAs between PD and T2DM

Through the intersection of mRNAs predicted by three miRNA-mRNA databases, we identified 85 hsa-miR-342-3p-related and 264 hsa-miR-630-related mRNAs. After eliminating duplicates, a total of 343 predicted downstream mRNAs were obtained. GO and KEGG analyses revealed that these DE-miRNAs were primarily involved in the regulation of transcription from RNA polymerase II promoter, DNA-templated regulation, cell proliferation, NF-Kappa B signaling, and NLRP3 inflammasome complex assembly in BP (Fig. 3A). The MF of DE-miRNAs was enriched in protein binding, metal ion binding, ATP binding, and DNA binding (Fig. 3B). The CC analysis indicated that the predicted downstream mRNAs were mainly located in the nucleus, cytoplasm, cytosol, nucleoplasm, and membrane (Fig. 3C). Additionally, KEGG analysis demonstrated that DE-miRNAs were primarily associated with the Ras signaling pathway, PI3K-Akt signaling pathway, p53 signaling pathway, and MAPK signaling pathway (Fig. 3D).

3.3. Validation of miRNA-targeted mRNAs

Using the GSE16134 dataset of PD, we verified the predicted downstream mRNAs. A total of 909 DEGs, including 564 up-regulated and 345 down-regulated genes, were identified. By intersecting predicted mRNAs with DEGs, we selected 21 DE-targeted mRNAs (Fig. 4A–C). The screened miRNA-mRNA network is shown in Fig. 4D. Genetic correlation analysis revealed a strong positive

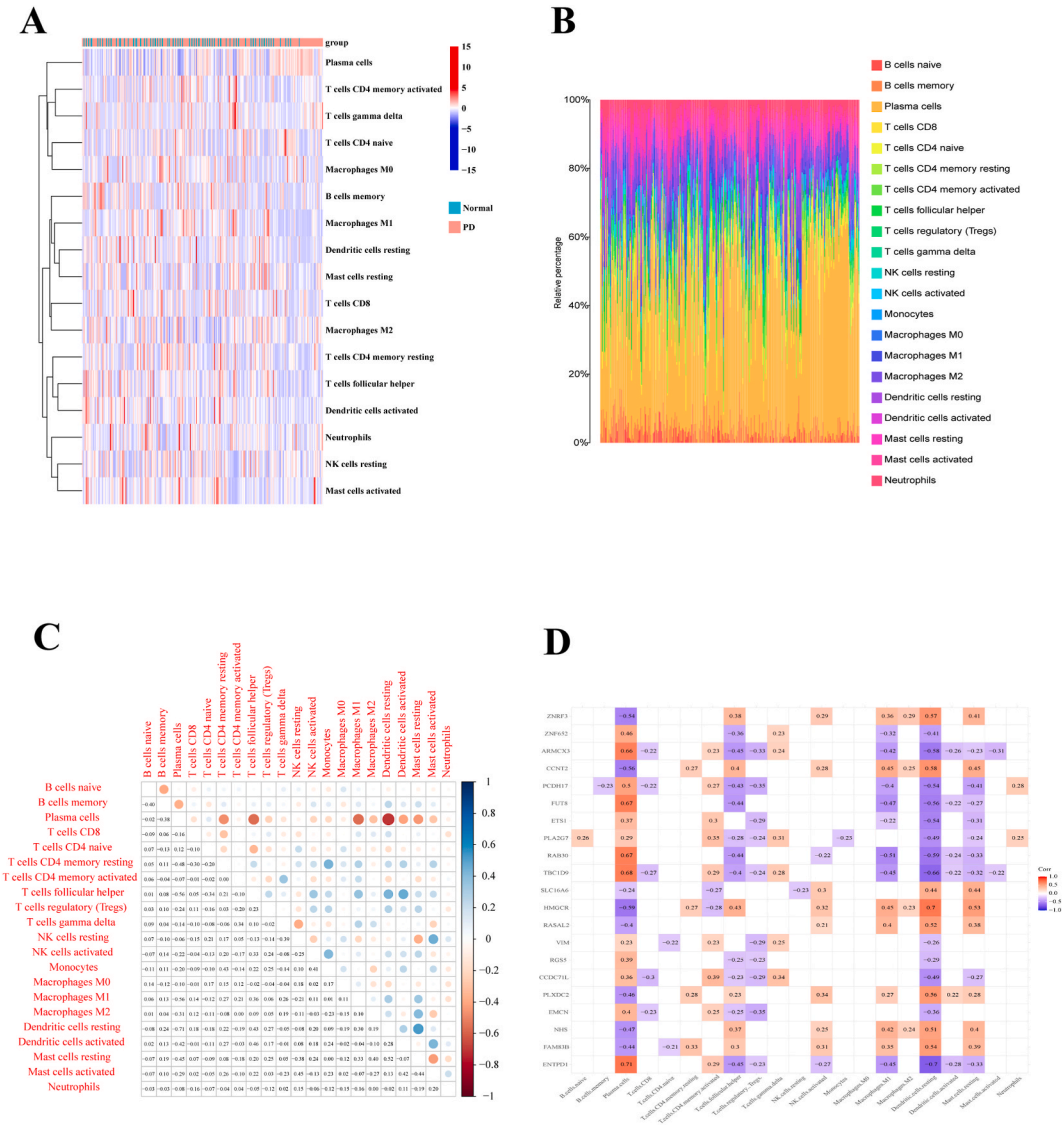

Fig. 5. Immune infiltration analysis of 21 DE-miRNA-targeted mRNAs. **(A)** Heatmap of immune cell expression in PD. **(B)** The immune cell content of each sample in PD. **(C)** Correlation between immune cells in PD. **(D)** Correlation between immune cells and 21 DE-miRNA-targeted mRNAs in PD.

correlation (p-value <0.05) between HMGCR and CCNT2 (Fig. 4E). According to functional enrichment analysis by the Metascape online tool, these 21 DE-targeted mRNAs were mainly involved in the RHO GTPase cycle, nucleobase-containing small molecule metabolic processes, and enzyme-linked receptor protein signaling pathways (Fig. 4F).

3.4. Immune infiltration analysis

To comprehend the role of immune infiltration in PD and the correlation between miRNA-targeted mRNA and immune infiltration, the "Cibersort" R package was employed for immune infiltration analysis. The expression and composition of various immune cells in gingival tissue samples from PD are illustrated in Fig. 5A and B, respectively. The correlation analysis between immune cells in PD is shown in Fig. 5C. Plasma cells exhibited a strong positive correlation with dendritic cells resting. Additionally, the selected DE-miRNA-targeted mRNAs were primarily associated with plasma cells, T cells follicular helper, macrophages M1, dendritic cells resting, and mast cells resting (Fig. 5D).

3.5. Identification of hub DE-miRNA-targeted mRNAs

To further identify hub DE-miRNA-targeted mRNAs, we employed a machine learning method. We screened 7 genes identified by lasso regression and the top 10 genes identified by RF (Fig. 6A, B, and C). Ultimately, 3 common genes (ENTPD1, PLXDC2, and RASAL2) were considered as the hub DE-miRNA-targeted mRNAs (Fig. 6D). The mRNA expression of these three genes in the GSE16134 dataset is depicted in Fig. 6E. Validation using another transcript sequencing dataset of PD confirmed consistent changes in these three genes, all statistically significant (Fig. 6F).

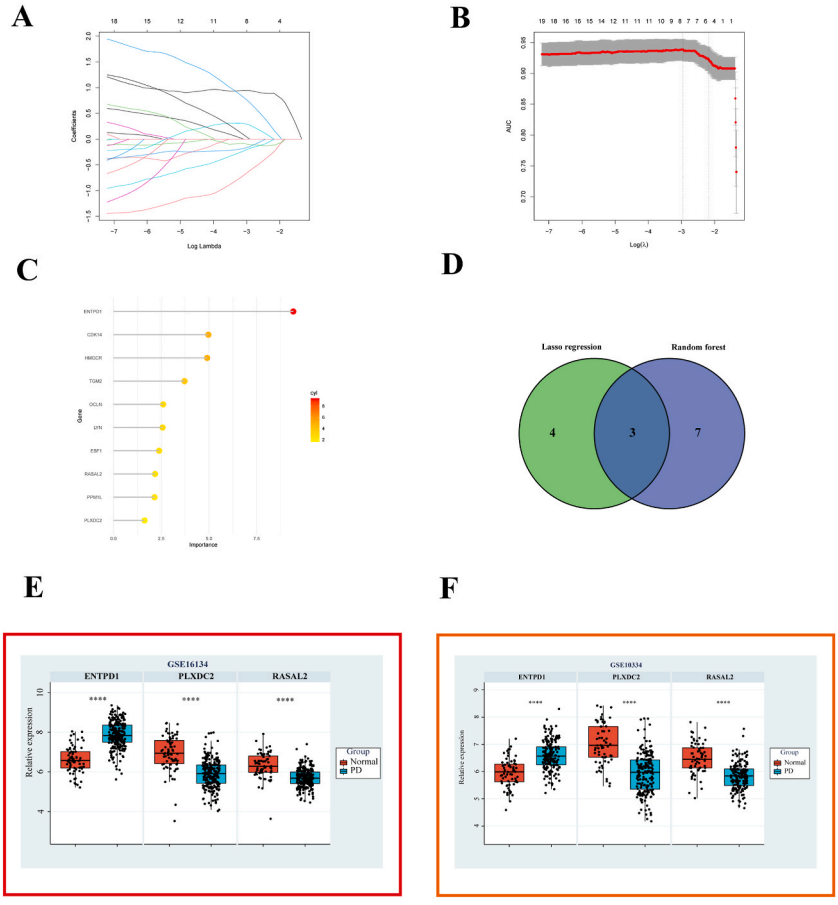

Fig. 6. Identification of hub DE-miRNA-targeted mRNAs by machine learning. **(A, B)** hub genes screening in the lasso model. **(C)** The lollipop chart shows the top 10 important genes calculated by random forest algorithm. **(D)** Venn diagram of lasso regression and random forest algorithm. **(E)** The relative expression of hub DE-miRNA-targeted mRNAs in PD training set. **(F)** The relative expression of hub DE-miRNA-targeted mRNAs in PD test set. ****p < 0.0001.

3.6. Clinical correlation and related pathway of hub DE-miRNA-targeted mRNAs

ROC analysis results in two PD datasets indicated that ENTPD1, PLXDC2, and RASAL2 exhibited superior diagnostic efficacy for PD (Fig. 7A and B). Additionally, we analyzed the relationship between hsa-miR-342-3p and hsa-miR-360 and clinical disease status. Hsa-miR-360, but not hsa-miR-342-3p, was associated with the course of PD and the area of invasion (p-value <0.05) (Fig. 7C and D). Hsa-miR-360 increased in chronic PD and decreased in generalized PD. To further discern the roles of the three hub DE-miRNA-targeted mRNAs, we explored their related pathways in humans through the KEGG database and found that ENTPD1 was involved in DNA metabolism pathways, while RASAL2 was associated with the Ras signaling pathway (Fig. 7E).

4. Discussion

As a complication of T2DM, PD lacks effective early diagnosis and treatment targets. The current consensus attributes the mechanism of T2DM promoting the onset and progression of PD to the increased presence of inflammatory factors such as TNF-α and interleukin 14 (IL-14). However, the specific mechanism and related pathways remain incompletely elucidated [17]. miRNA, a recent

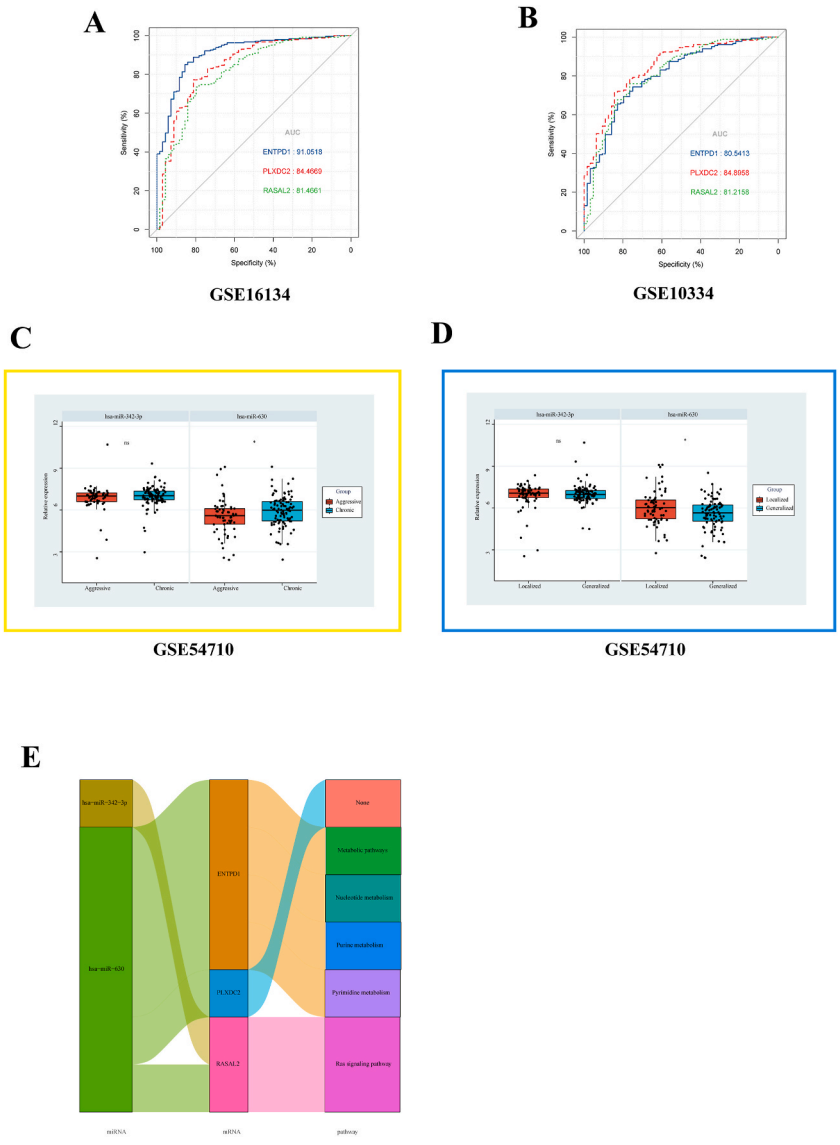

Fig. 7. Clinical correlation analysis of hub DE-miRNA-targeted mRNAs. **(A)** ROC curve of hub DE-miRNA-targeted mRNAs in PD training set. **(B)** ROC curve of hub DE-miRNA-targeted mRNAs in PD test set. **(C)** The expression difference of 2 DE-miRNAs in aggressive and chronic PD group. **(D)** The expression difference of 2 DE-miRNAs in localized and generalized PD group. **(E)** The relationship of DE-miRNA-mRNA and pathways. ns $p > 0.05$; *$p < 0.05$.

research hotspot in the context of T2DM and PD, holds promise as a target for disease discovery and intervention. Therefore, our objective was to unravel the molecular mechanism through which T2DM contributes to PD by identifying common miRNAs associated with both conditions.

We conducted an analysis of common differentially expressed miRNAs (DE-miRNAs) between serum samples from T2DM patients and gingival tissue samples from PD patients. This analysis, combined with the transcriptome dataset of PD gingival tissue, enabled the screening of DE-miRNA-targeted mRNAs. We explored the functionality of these DE-miRNAs through functional enrichment analysis and immune cell infiltration analysis. Additionally, machine learning techniques were employed to identify key targeted genes and analyze their pathways and clinical relevance.

Our findings revealed that T2DM and PD shared two common miRNAs, namely hsa-miR-342-3p and hsa-miR-630, suggesting a potential mechanistic link between T2DM and PD. Both miRNAs were up-regulated in both T2DM and PD. Studies have shown that overexpression of hsa-miR-342-3p can reduce the release of inflammatory cytokines TNF-α, cyclooxygenase-2, IL-6, and IL-1β in DM, key factors believed to promote PD in T2DM [23]. Furthermore, hsa-miR-342-3p was negatively correlated with the mRNA of the cytokine receptor CXCR2, which plays a role in transporting inflammatory mediators [24]. High blood sugar can reduce the expression of hsa-miR-342-3p in endothelial cells, an obesity-related miRNA [25]. However, we observed that it was up-regulated in T2DM and PD, which may be related to the increased protective effect of stress. Hsa-miR-630, primarily studied in tumors, exhibited a bidirectional effect on tumors, with its role in T2DM and PD yet to be reported [26,27]. Functional enrichment analysis indicated that these two miRNAs were involved in NF-kappa B and NLRP3, consistent with previous findings on hsa-miR-342-3p. The exploration of their potential roles revealed associations with Ras, PI3K-Akt, P53, and MAPK signaling pathways, known to be related to inflammation.

By integrating the PD transcriptome dataset and employing machine learning, we identified three DE-miRNA-targeted mRNAs (ENTPD1, PLXDC2, and RASAL2). Among these, ENTPD1 was up-regulated in PD, while PLXDC2 and RASAL2 were down-regulated. Previous studies have reported the protective role of ENTPD1 in sepsis through consistent IL-42α secretion, emphasizing its significance in anti-inflammation [28,29]. The action of ENTPD1 is linked to its encoding of ATP [30]. Two single nucleotide polymorphisms of PLXDC2 are associated with the progression of T2DM and can aid in predicting the clinical course of T2DM in high-risk patients [31]. RASAL2 (RAS protein activator like 2), a RASGTPase activating protein, is mainly involved in Ras signaling pathway and regulation of AMPK mediated autophagy [32]. Both Ras signaling pathway and autophagy are well-documented in their roles in inflammation [33,34]. We found that both hsa-miR-342-3p and hsa-miR-630 target RASAL2. In addition, inflammatory factors such as NF-κB aggravate cell damage by increasing RASAL2 expression [35]. Our study revealed a decrease in RASAL2 in PD, potentially linked to the protective elevation of hsa-miR-342-3p and hsa-miR-360 inhibiting its expression, thereby shielding cells from inflammatory damage. The overexpression of these two miRNAs may hold the potential to reverse inflammatory damage in PD, a hypothesis that warrants further experimental validation.

Although we have identified a miRNA-mRNA regulatory network linking PD and T2DM based on bioinformatics analysis, this study still has certain limitations. Firstly, the data used in this study were sourced from gingival tissues of PD patients, while miRNA data from blood samples of PD patients might yield better insights. Secondly, there is a lack of further clinical information regarding the patients. Lastly, our study is confined to data analysis, and the miRNA-mRNA network and their function should be validated through in vitro and in vivo experiments.

In summary, employing bioinformatics methods and machine learning algorithms, we identified common miRNAs in T2DM and PD, shedding light on their potential roles in PD.

5. Conclusion

By combining miRNA sequencing data of T2DM and PD, we found that hsa-miR-342-3p and hsa-miR-360 may be early warning targets of T2DM promoting PD, and hsa-miR-342-3p-/hsa-miR-360-RASAL2, hsa-miR-360-ENTPD1/PLXDC2 axis plays an important role in PD. This study presents a novel target for T2DM in promoting the diagnosis and treatment of PD.

Data availability statement

The datasets GSE54710, GSE185845, GSE16134, GSE10334 and GSE173078 are available from GEO database (https://www.ncbi.nlm.nih.gov/geo/).

Ethics declarations

Review and/or approval by an ethics committee was not needed for this study because the study used anonymized, published data.

CRediT authorship contribution statement

Shaobing Yu: Writing – review & editing, Writing – original draft, Visualization, Software. **Ruxin Wang:** Writing – review & editing, Writing – original draft, Software. **Wei Wang:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

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